Drug Corner

Long COVID : New Treatment Perspective Using Nutraceuticals

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Coronavirus disease (COVID-19) is an ongoing worldwide pandemic affecting a large population regardless of gender, age, and ethnicity. The persistence of the COVID-19 symptoms has become a significant health issue and is collectively called "Long COVID." It can be described as the presence of symptoms of COVID even after the recovery from the viral infection. The prolonged symptoms in the patients could be due to various reasons and factors. Prolonged fatigue is a common symptom of Long COVID in patients even after they have recovered from the viral infection. Currently, only rehabilitation has shown promising results in managing the symptoms of Long COVID. Although pharmaceutical drugs have shown potential in treating the symptoms of Long COVID, more clinical evidence is required to confirm its treatment with less to no side effects; since it's a new disease, the in-depth knowledge of the same is still evolving. Another healthier approach to treating the symptoms of Long COVID could be dietary supplements or "Nutraceuticals," identified as an alternative to pharmaceuticals, including nutritional supplements, derived nutrients, and dietary and herbal products that display physiological advantages. Nutritional strategies can also play a role in treating hospitalized patients as maintaining the immune system is critical to combat viral infection.Nutraceuticals may be a practical and healthier approach to managing the symptoms of Long COVID or COVID-19. Although ample clinical evidence is present for the treatment of symptoms of COVID-19, further studies in treating Long COVID or its symptoms are required.

[*J Indian Med Assoc* 2022; **120(5):** 67-74]

Key words **: Long COVID, Headache, Pain, Curcumin, Ginger, Nutraceutical etc.**

Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), a virus that first appeared in December 2019, led to an ongoing pandemic[1]. A pathogenic virus causing severe respiratory issues. It has been reported as a significant ongoing pandemic that has cost millions of lives worldwide. Around 80% of the population has experienced mild to moderate symptoms of COVID-19, and among those who experienced the disease in severity, 5% were victims of critical illness[3]. It was noted that the virus primarily causes gastrointestinal and respiratory tract infections. A small number of clinical trials have reported the active virus, and fecal dissemination has been detected in some patients[2]. A new development that was observed was the persistence of the COVID -19 symptoms that lasted up to weeks or even months; called "Long COVID," "Long Haulers," or "Post COVID syndrome"[2].

Editor's Comment :

- The transmission of acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is fatal as it affects thousands of people daily and can produce long COVID symptoms even after the treatment. The management of long COVID symptoms after COVID is difficult as no definitive therapy is available, and symptoms varies from patients to patients. Nutraceuticals such as CoQ-10, Ginger, Zinc, n-acetylcysteine etc. found to be effective in the treatment of symptoms observed in Long COVID. Current review article helps to identify symptoms occurring during long COVID and the role of nutraceuticals in their management.

LONG COVID-19 :

The persistent presence of symptoms of COVID-19 can be termed "Long COVID" or "Post COVID syndrome."The symptoms can last from weeks to months after acquiringSARS-CoV-2 infection, irrespective of the viral status (Fig 1). It can be continuous or relapsing and remitting in nature. The relative symptoms are not limited to just one, as this viral infection is still an ongoing pandemic; we still lack in-depth knowledge of the working of the virus in the body and any other new budding symptom that could randomly pop up. COVID-19 illness is poorly understood because it affects survivors at all disease severity levels, including younger adults, children, and those not hospitalized[5]. The most observed post-COVID symptoms are fatigue, dyspnoea, olfactory and gustatory dysfunction, chest pain, myalgia, and sleep and mental disorders[4]. The possible working of how the virus affects the body could be that the virus invades

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Received on : 07/05/2022
Accepted on : 11/05/2022

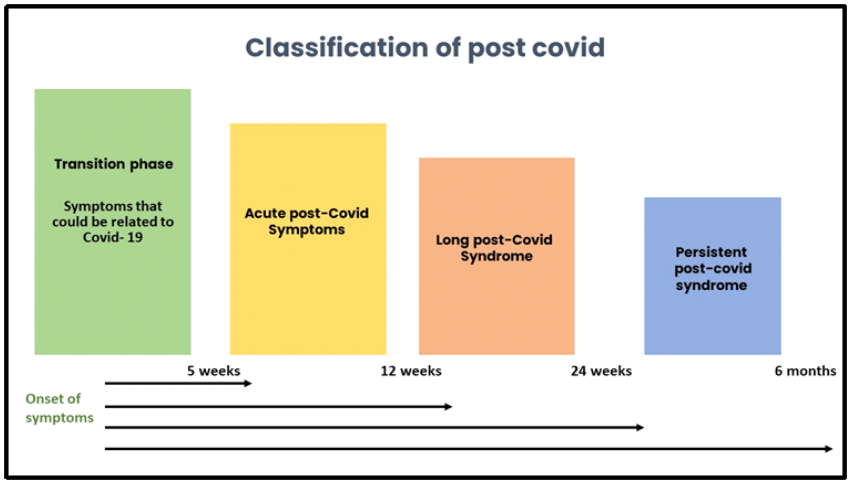

Fig 1 — Classification of Long COVID

many tissues and has a multiorgan and multisystem impact. Angiotensin-Converting Enzyme 2 (ACE2) receptor is expressed in many tissues, leading to oxidative stress and inflammation, leading to weak immunologic response, and incomplete virus eradication[5,6]. Long hauler's symptoms should not be ignored in patients, and proper care should be sought as soon as possible to help them achieve a better quality of life. A personalized and comprehensive approach to manage the symptoms is advised[9].

Prevalence of Long COVID :

The heterogeneous nature of long covid has made it difficult to estimate its prevalence, thereby lacking a precise case definition[1]. A patient-led survey found that the European population was suffering self-reported long covid. Among the patients who reported Long COVID, over 697,000 were suspected of having COVID-19 at least 12 weeks previously.Studies suggest that the symptoms of Long COVID may persist forsix months to over a year. The patients aged 35-49 or 50-69 were more prone to experience these symptoms. The prevalence rate was statistically significantly higher in females (1.9%) than in males (1.5%). Moreover, health and social care workers demonstratedthe highest prevalence rates of self-reported long COVID[11].

Clinical manifestation :

Long-term COVID may occur due to lasting tissue damage (eg, lung, brain, and heart) and pathological inflammation (eg, viral persistence, immune dysregulation, and autoimmunity). Prolonged inflammation could be the significant reason forneurological and cognitive dysfunctions in the body, along with several other symptoms.A diverse array of less prevalent symptoms and signs, including sweating, chest pain, sore throat, anxiety, and headaches, have also been reported[1]. Frequently observed symptoms include cognitive and mental impairments, chest and joint pains, palpitations, myalgia, smell and taste dysfunctions, cough, headache, and gastrointestinal and cardiac issues. Less frequently observed symptoms were sweating, chest pain, sore throat, anxiety, headaches, joint pain, hair loss, etc[3]. One bemusing factor about long covid is that patients who have recovered from COVID -19 are more prone to it[8]. Children are also vulnerable to developingLongCOVID, including those who wereinfected with asymptomatic COVID-19. The symptoms seenin children were dyspnoea, fatigue, myalgia, cognitive impairments, headache, palpitations, and chest pain that lasted for at least six months[9]. The most common symptom of Long COVID was fatigue ranging from 17.5% to 72% among hospitalized patients, which persistedeven after seven months resulting in severe disability[10].

Pathophysiology of Long COVID :

How Long COVID affects the host remains unclear. However, possible speculation suggests that the persistence of infection is due to viremia in patients with modified immunity, re-infection, or relapse[11]. The continuation of symptoms can be the consequence of organ damage, the degree of the organ damage and the time it would be required to recover from the injury, (chronic inflammationor immune response/ autoantibody generation, rare persistence of the virus in the body, the nonspecific effect of hospitalization, sequelae of critical illness, post-intensive care syndrome complications related to comorbidities) or adverse effects of medications used[12]. An unresolved source of inflammation could be in the gut. It was observed thatthe COVID virus could replicate in the gut quite efficiently due to the elevated levels of ACE2 receptors, thus leading to increased fecal shedding of SARS-CoV-2 in patients (Fig 2)[13].

The other possible mechanisms of Long COVIDcan be classified into :

- Persistent tissue/organ injury following the acute phase.
- Other unresolved, ongoing, or recurrent reactions without evidence of classically recognized tissue/organ injury. Table 1 describes the possible mechanisms involved in Long COVID[14].

Table 1 — *Possible mechanisms involved in Long COVID*

S. No	System	Involved Symptoms	Possible mechanism
1	Neurologic	Headache and pain	• Inflammation in various tissues can lead to aggravation of tissue damage in joints and muscles and trigger pain-related symptoms. • Activation of nerves can lead to vasculopathy i.e., unbalanced vasoconstriction, oxidative stress, Nerve viral invasion, hypoxia, and pro-inflammatory cytokines. • Neurological complications leading to pain such as a stroke, Guillain Barré syndrome, and myelitis. • Glymphatic-lymphatic system congestion hypothesis. olfactory nerves damage might lead to a reduced outflow of cerebrospinal fluid through the cribriform plate, toxic build-up within the CNS, congestion of the lymphatic system with secondary cranial hypertension.
		Olfactory Dysfunction	• Viral invasion • Subsequent cell inflammation and injury • Presence of ACE2 in epithelial cells of olfactory mucosa (Mechanism unclear)
		Persistent fatigue	• Neuro-inflammation and subsequent neurotransmission disorders • Psychological factors (neurotransmitters levels can vary after COVID-19 and give • rise to psychological disorder accounting for fatigue worsening) • Peripheral factors (musculoskeletal impairment) in chronic fatigue • Environmental factors (social isolation temperature, humidity) • Mitochondrial dysfunction leading to Bioenergetic disorders (muscle)
		Psychiatricdisorders (anxiety, depression, trauma-related disorders)	• Persistent inflammatory process secondary to the viral invasion or dysregulated immunity processes can cause brain dysfunction neuronal injury leading to: ✓ The blood-brain barrier (BBB) is disrupted by the Pro-inflammatory cytokines which increase its permeability to cytokines and leucocytes transmigration • Inflammation processes may induce: • Activation of the coagulation and the formation • of micro thrombosis impairing tissue vascularization and neurotransmission due to the release of cytokines. • Potential involvement of gut-brain axis • Metabolic brain disorder: ✓ Mitochondrial dysfunction leads to reduced energy metabolism and neuro-inflammation ✓ Cytokine-induced activation of IDO-1 leads to depression. ✓ Virus residual: incomplete immune response causes residual virus, and/or antigen load remains to contribute to a low-grade smoldering inflammatory response. • Autoimmunity: Inflammatory can favor an aberrant immune response against the nervous system • Secondary brain disorder: Indirect nervous system damage via the systemic complications of acute illness (Haemodynamic and coagulation disorders, arrhythmia, severe systemic inflammation, delirium)
2	Cardiorespiratory	Cardiorespiratory dysautonomic symptoms (palpitations, post-exertional malaise, exercise intolerance,breathlessness, chest pain)	• Disruption of the autonomic nervous system (autoimmunity, microcirculation disorders) due to virus or immune dysfunction leading to various symptoms such as dizziness andother cardiovascular symptoms, hypoperfusion of different organs
3	cardiovascular	Thromboembolic complications (Stroke, pulmonary embolism)	• These cardiovascular issues can lead to chronic symptoms, associated with organ damage: • Direct complement activation (inflammation)loss of endothelial homeostasis and integrity • viral-induced activations of platelets (ACE2 receptor) leading toinflammation and coagulation activation • Antiphospholipid antibodies • Systemic cytokines release leading to coagulation activation
		Heart disorders (Impaired contractility, dyspnoea, arrhythmia)	• Residual inflammation could lead to fibrosis • Interactivity with adipose tissue of epicardium points towards long-term arrhythmia and coronary disease • Heart tissue inflammation and account for contractility impairment:acute or subacute myocarditis
4	Respiratory system	Dyspnoea, Cough, Chest pain, Exercise limitation	• Pulmonary alveolar inflammation after the viral invasion • Degeneration of alveolar epithelial lining with the emergence of hyaline membranes • Excessive cytokines production (host inflammatory response) and enhanced influx of inflammatory cells • Decreased expression of ACE2 receptor and angiotensin 1,7 peptides • Greater oxidative and contribute to inflammation and fibrosis stress due to high supplemental oxygen concentration • Unresolved (micro-) vasculature damages may be a potential precursor to chronic thromboembolic disease and pulmonary hypertension.
5	Immune system	Wide range of symptoms	• Inflammation could be responsible for persistent symptoms • Autoimmunity phenomena may result from inflammation and dysregulated immune responses. • Genetic polymorphism in the cytokine genes' regulatory regions can account for inter-individual differences in the severity and occurrence of symptoms • Mast cell activation syndrome hypothesis: The mast cell would be activated via the release of the cytokine. This could lead to lung fibrosis via stimulation of fibroblast activity. • The natural downregulation of the strong initial inflammatory response could allow the virus to persist and replicate in the body with ongoing inflammation and autoimmunity phenomena.
6	Gastro-intestinal and hepato-biliary system	Gastrointestinal symptoms: anorexia, dyspepsia, nausea/vomiting diarrhea abdominal pain	• Hypothesis of the gut as an undetected virus reservoir • Contributions of genetic predisposition and interaction between the gut and environmental and psychological factors • Viral invasion-local inflammation followed by leucocytes infiltration in the digestive mucosa generating a local inflammation • Immune-mediated disruption leading to gut motility disruption
7	Multisystem Inflammatory Syndrome in Children (MIS-C)	Fever, Multiple organ dysfunction, Mucocutaneous Disorders, Abdominal Symptoms, Cardiovascular disorders, Neurological disorders	• Genetical predisposition host factors • Uncontrolled T-cell immune response (triggered by SARS-CoV-2) • Complement activation • Molecular mimicry between antigens and host tissues.
8	Musculoskeletal system	Muscular weakness, Bone and joint disorders (pain, mobility)	• **Muscle:** ✓ Pro-inflammatory cytokines-induced disruption of myocytes ✓ Cytokines-induced muscle fibroblast activation leads to fibrosis ✓ Neuronal demyelination • **Bone:** ✓ leukocyte aggregation, and vessel inflammation that contributes to the development of osteonecrosis • **Joints:** ✓ Autoimmunity (virus persistence, dysregulated immune response, triggering of connective tissue diseases) and NETs activation
9	Endocrine system	Thyroid disorders Diabetes	• **Thyroid** ✓ Direct damage to the thyroid gland ✓ Low-T3 syndrome in hospitalized subjects (inflammation due to severe COVID-19) ✓ Subacute thyroids • **Diabetes** ✓ Possible viral invasion of the pancreatic β cell that precipitates new-onset diabetes

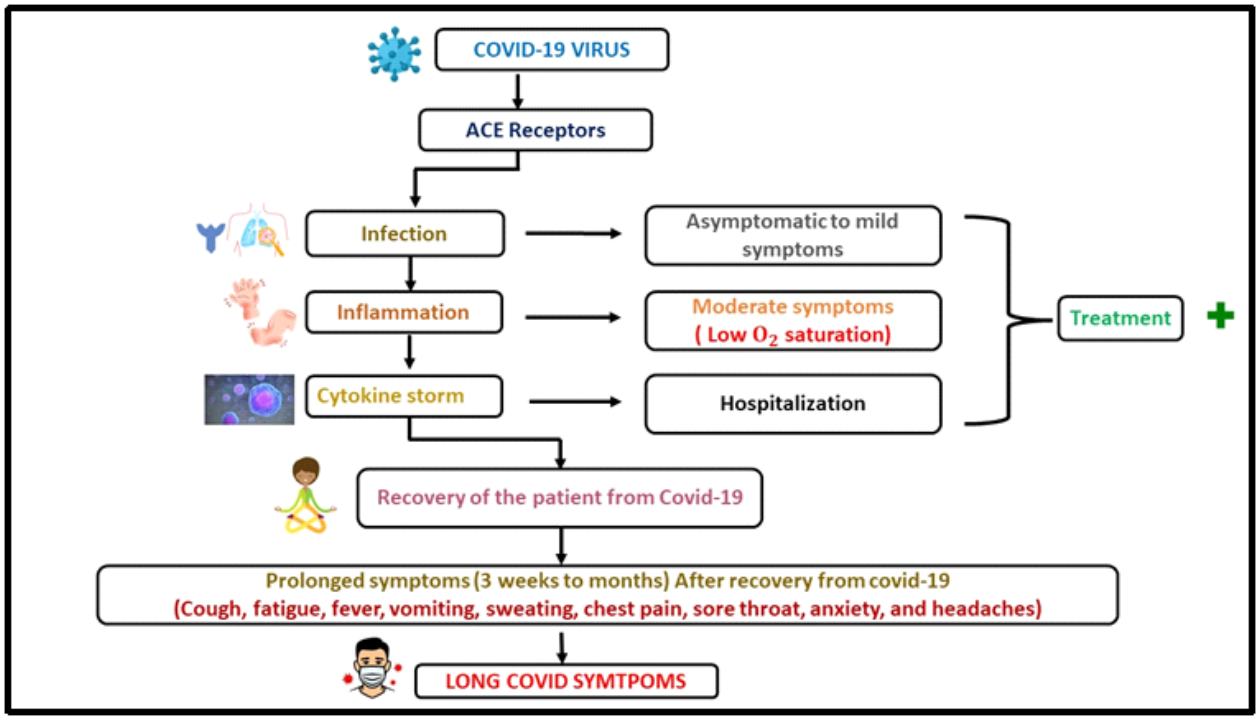

Fig 2 — Pathophysiology of "Long COVID[2]

Possible Risk factors :

Major risk factors include female sex, more than five early symptoms, early dyspnoea, prior psychiatric disorders, and specific biomarkers (eg, D-dimer,C-Reactive Protein (CRP), and lymphocyte count)[3]. Patients who had more than five symptoms in the first week of COVID-19 were four times more vulnerable to developing Long COVID. Fatigue, headache, shortness of breath, hoarse voice, myalgia, older people, and obese patients were more susceptible to Long COVID[15].

Biomarkers :

Among COVID-19 survivors, the risk factors for pulmonary dysfunction were elevated Blood Urea Nitrogen (BUN) and D-dimer levels[16]. Radiological abnormalities of the heart, liver, and kidney were correlated to inflammatory markers such as CRP, procalcitonin, and neutrophil count[17]. Increased D-dimer and CRP levels and decreased lymphocytes were more common in long COVID-19[18].

Mental health :

Post-traumatic Stress Disorder (PTSD) and psychological distress were common in health workers compared to patients suffering from Long COVID. The higher the exposure,the greater the incidence of subsequent PTSD. Young women and those carrying heavy responsibilities and concern for others are more bound to develop Post-traumaticsymptomatology (PTS) following COVID-19 exposure, and hence, they deserve more attention[29].

POTENTIAL INTERVENTION :

Rehabilitation :

Rehabilitation includes various breathing exercises to strengthen respiratory muscles, especially the diaphragm. Positive outcomes of rehabilitation were observed for the treatment of Long COVID patients. Patients were advised to practice light aerobic exercises accordingly to their possible capacity. The exercise level was gradually increased until improvements in fatigue and dyspnoea wereobserved. Physical rehabilitation has its drawbacks, too[18], which should be considered. Rehabilitation may not be suitable for all critical COVID-19 survivors, especially those with serious pulmonary or cardiac damage[20].

Pharmaceutical treatment :

Pharmaceutical drugs are used to manage specific symptoms such as fever; however, drugs having similar treatment properties might hold the potential to be repurposed for Long COVID. At the same time, no pharmaceutical drug ameliorates or attenuates the symptoms of Long COVID so far[20]. Collective studies have proposed that mast cell activation syndrome (MCAS) may also underlie Long COVID pathophysiology; studies have shown to trigger inflammatory mast cell responses alongside other immune cells in COVID-19 patients[23]. Another hurdle

in the treatment approach is the heterogeneous nature of Long COVID, which involves multiple subtypes complicating the accurate diagnosis[3].

Nutraceuticals :

Nutraceuticals are the combination of nutrition and pharmaceuticalsthat popularly speculate about food and its medicinal benefits[22]. They are one of the promising new alternatives to pharmaceuticals that may include nutritional supplements, derived nutrients,and dietary and herbal products that display substantial physiological advantages that potentially could play a significant role in reversing many inflammatory surrounding diseases[23]. Besides the conventional treatments, nutraceuticals could be highly beneficial in treating and preventing COVID-19[22].

The nutraceuticals that could benefit in long covid are **:**

***Coenzyme Q10 (CoQ10)* —** It is rich in antioxidants, prevents oxidative stress, mitigates hyper-immune response, and directly inhibits viral replication and entry[24]. CoQ10 attenuates the action of genes involved in inflammationand controls the release of pro-inflammatory cytokinesin various disorders[25]. It also assists in the regeneration of other antioxidants. In addition, it is a crucial factor in the respiratory chain of the inner mitochondrial membrane and is very much vital to energy metabolism.A double-blinded, placebo-controlled, three crossover study was conducted. The study included 17 healthy volunteers who were randomized to receive oral supplementation of Coenzyme Q10 (100 or 300 mg/d) or placebo administration for eight days. Subjects were made to perform workload trials on a bicycle ergometer at fixed workloads twice for two hours and then were made to rest for four hours. During the physical tasks, subjects performed non-workload trials with maximum velocity for 10 s at 30 min (30-min trial) after physical tasks and 30 min before the end of the tasks (210-min trial). Oral CoQ10 supplementation improved subjective fatigue sensation and physical performance during fatigue-inducing workload trials[26]. The protective role of CoQ10 in improving viral myocarditis and drug-induced cardiotoxicity introduces this supplement as an appropriate choice for the prevention of COVID-19 cardiovascular complications, which are generally influenced by two factors: cytokine storm and adverse effects of the medications. The hyper-cytokinemia caused by SARS-COV-2 infection could lead to fulminant myocarditis, a lethal condition caused mainly by a hyper-inflammatory state and cytokine storms, particularly during viral infection[27,28].Another randomized controlled multicentre trial was conducted on 420 patients with moderate to severe Heart Failure (HF). The patients were randomly assigned in a 2-year prospective trial to receive CoQ10 100 mg 3 times daily or placebo, in addition to standard therapy. The test results demonstrated that long-term CoQ10 treatment of patients with chronic HF was safe, improved symptoms, and reduced major adverse cardiovascular events[29]. Studies suggest that CoQ10 crossesthe Brain Blood Barrier (BBB) easily. CoQ10 can reduce oxidative stress and modulates immunologic reactions as a neuroprotective agent. These properties may help to reduce CNS inflammation and prevent BBB damage and neuronal apoptosis in COVID-19 patients[30-32]. Similarly, CoQ10 could improve the interference in the RASsystem caused by COVID-19 infection by exerting anti-Angiotensin II effects and decreasing oxidative stress. The antihypertensive effects of CoQ10 are not entirely confirmed, and more well-designed clinical trials are needed to verify it. Moreover, CoQ10 can not solely reduce blood pressure but could be beneficial against hypertension in the context of metabolic diseases like diabetes as adjunctive therapy to adjust blood pressure[33,34].

***Ginger* —** Ithas anti-inflammatory and antiviral properties, making it beneficial in treating COVID-19 symptoms[22]. A clinical trial with suspected COVID-19 outpatients as participants was conducted. The results of the studydemonstrated that Zingiber officinale and Echinacea alleviated and controlled the clinical symptoms in COVID-19 outpatients[35].

***Glutathione* —** Glutathione (GSH) exerts anti-inflammatory effects by inhibiting ACE activity, decreasing Reactive Oxygen Species (ROS) production, and inhibiting NF-kB activation. The oxidized form of glutathione (GSSG), renin, and viral infection shift the ACE/ACE2 balance toward ACE. Data from a published report suggests thatfor two COVID-19 patients, 2 g of PO or IV glutathione improved the dyspnea within one hour of use, and it regularly alleviated respiratory symptoms[36].

***Zinc* —** It is the second abundant trace element and an essential dietary supplement used to preserve immunity. Zinc helps treat upper respiratory tract viral infection and hence can also be beneficial in managing COVID-19. Moreover, it may also inhibit the attachment of the virus to nasopharyngeal mucosa and inhibit viral replication. In vitro studies have demonstrated that zinc may inhibit template binding and elongation of SARS-COV-1 RNA-dependent polymerase, which helps prevent viral replication. A studyshowed that patients with COVID-19 who had zinc deficiency required more corticosteroid management and were also associated

with a prolonged hospital stay[22]. Moreover, the reports suggest the use of zinc salt in managing the COVID-19 symptoms[37].

Curcumin — It is Turmeric's active ingredient that has anti-inflammatory properties. In clinical trials, curcumin has been shown to be an effective treatment for COVID-19[38]. The intervention of nano-curcumin resulted in a significant increase in the mRNA expression and cytokine secretion of IL-1β, IL-6, TNF-α, and IL-18 in the COVID-19 patients. Ultimately, nano-curcumin may modulate inflammatory cytokines and cytokine secretion in COVID -19 patients, leading to an overall recovery[39].

N-Acetylcysteine (NAC) — Glutathione is a cofactor for various peroxidase enzymes and a catalyst in reactions that reconvert oxidized cysteine groups to their native form. NAC can enhance the production of glutathione. N Acetyl l cysteine increases the influenza virus-specific lymphocyte proliferation and interferon (IFN) γ production at a concentration of 1.0 mmol/l. Furthermore, N acetyl l cysteine enhanced a specific activity of two influenza-specific CD8+ cytotoxic T lymphocyte clones directed towards HLA A*0201 and HLA B*2705 restricted epitopes[40]. In a clinical trial conducted on COVID-19 patients, NAC helped significantly lower the influenza-like symptoms, which resulted in a shorter hospital stay. Likewise, NAC supplementation could be beneficial in reducing the severity of the illness.

Vitamin D3 — Besides known antimicrobial and anti-inflammatory effects, vitamin D metabolites directly impact ACE2, which serves as the cell surface entry receptor for SARS-CoV-2 infection. In preclinical studies, vitamin D metabolitesincrease ACE2 expression in pulmonary microvascular endothelial cells. Although increased ACE2 expression may theoretically increase viral entry into cells, it may benefit the already infected patients because SARS-CoV-2–mediated downregulation of ACE2 may perpetuate lung injury[41]. A randomized clinical trial on reverse transcriptase-polymerase chain reaction (RT-PCR) SARS-CoV-2 positive adults was conducted. 5000 IU daily oral vitamin D3 supplementation reduced the time to recoverfrom cough and gustatory sensory loss among patients with suboptimal vitamin D status and mild to moderate COVID-19 symptoms. Moreover, Vitamin D3 supplementation could serve as adjuvant therapy for COVID-19 patients[42].

Vitamin C — Vitamin C or ascorbic acid is a water-soluble vitamin that possesses antioxidant, anti-inflammatory, and immunomodulatory properties. It acts as an enzyme cofactor for several biosynthetic processes and may increase the endogenous synthesis of catecholamines[22]. A randomized clinical study conducted on hospitalized critically ill COVID-19 patients showed that vitamin C supplementation significantly increased the survival duration of COVID-19 patients during the post-supplementation period[43].

CLINICAL EVIDENCE :

Table 2 describes the clinical evidence of nutraceuticals in the management of COVID-19.

CONCLUSION :

COVID-19 is an ongoing pandemic mainly affecting the respiratory organs of patients. Long COVID or Post COVID is the persistence of symptoms after the patient has recovered from COVID -19 infection. Fatigue and various other symptoms such as dyspnoea, olfactory and gustatory dysfunction, chest pain, myalgia, sleep, and mental disorders were the most common symptoms of Long COVID. Currently, rehabilitation is the most promising approach tomanaging the symptoms of Long COVID. Similarly,nutraceuticals could be another healthier and potential intervention to manage the symptoms. In conclusion, our review highlights the potential benefits of a variety of nutraceuticals in treating COVID-19. Although ample clinical evidence is present for managing the symptoms of COVID-19, further studies are required to clarify their potential therapeutic value.

Acknowledgement : We want to acknowledge Dr. Parshuram Nivrutti Shendge & Intelli Med Healthcare Solutions for providing all the support for completing the manuscript.

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Table 2 — *Clinical evidence of nutraceuticals in the management of COVID-19*

Nutraceutical	Study design	No of subjects	Duration	Intervention	Results	References
Coenzyme Q10 (cardiovascular)	randomized controlled multicenter trial	420	2 years	CoQ10 100 mg 3 times daily or placebo, in addition to standard therapy.	Long-term CoQ10 treatment of patients with chronic HF is safe, improves symptoms, and reduces major adverse cardiovascular events.	(33)
Coenzyme Q10 (Fatigue)	A double-blinded, placebo-controlled, three crossover study	17	8 days	Coenzyme Q10 (100 or 300 mg/d) or placebo	Oral Coenzyme supplementation improved subjective fatigue sensation and physical performance during fatigue-inducing workload trials and might prevent unfavorable conditions because of physical fatigue	(34)
Ginger	Clinical trial	100	2 weeks	concurrent Zingiber officinale (Tablet Vomigone 500 mg II TDS) and Echinacea (Tablet Rucoldup I TDS) The control group only received the standard treatment (Hydroxychloroquine).	Zingiber officinale and Echinacea alleviated and controlled the clinical symptoms in COVID-19 outpatients	(35)
Glutathione	Case report	2		2000 mg of oral or IV glutathione, zinc, 40–50 mg per day, and Vitamin C 1–2 g TID	Oral and IV glutathione, glutathione precursors (N-acetylcysteine), and alpha-lipoic acid may represent a novel treatment approach for blocking NF-κB and addressing “cytokine storm syndrome” and respiratory distress in patients with COVID-19 pneumonia.	(36)
Zinc	Report	4	2 weeks	Patients 1,2 were treated with zinc citrate lozenges (23 mg of elemental zinc); patient 3, zinc citrate/zinc gluconate (23 mg); patient 4, zinc acetate (15 mg).	high dose supplemental zinc may have a role in the management of COVID-19	(37)
Curcumin	Randomized clinical trial	80	2 weeks	160 mg of Nano-curcumin in four 40 mg capsules and placebo capsules daily. Additionally, the covid-19 patients receivedBetaferon 300 ìg subcutaneously every other day until 5 days, Bromhexine 8 mg tablets every 8 h, and Atrovastatin 40 mg daily was also given to the patients.	Nano-curcumin can modulate the inflammatory cytokines, especially IL-1β and IL-6 mRNA expression and cytokine secretion in COVID-19 patients	(39)
Vitamin D3	A Randomized Clinical Trial	69	2 weeks	5000 IU oral vitamin or 1000 IU oral vitamin D3 (standard control) once daily	A significant increase in 25(OH)D levels in the 5000 IU group only, the 5000 IU group had a significantly shorter time to recovery (days) than the 1000 IU group in resolving cough	(42)
Vitamin C	A randomized clinical trial	120	2 weeks	one capsule of 500 mg of vitamin C daily	Vitamin C supplementation could potentially increase the survival duration of covid-19 patients	(43)

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